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Blood pressure variability: Epidemiological and clinical issues

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Abstract

Blood pressure variability (BPV) is a classical physiological phenomenon. This paper describes major epidemiological and clinical issues of BPV which may be important to understand the background of this interesting feature. In healthy subjects, BPV is a measure of hemodynamic condition and reflects function of autonomic nervous system. BP fluctuations result from the complex interaction between environmental stimulation, genetic factors and cardiovascular control mechanisms. Abnormal BPV is recognized in persons with a blurred dipping pattern (i.e. extreme dipping, non-dipping, reverse-dipping, morning surge of BP) or increased variations of day-time or night-time BP (high BP lability). Inappropriate BPV worsens the outcome, including increase in all-cause and cardiac mortality and incidence of cardiovascular events, and advance in target organ damage. Abnormal BPV may be softened or removed with suitable time-dependent administration of anti-hypertensive agents, especially those acting on the renin–angiotensin system. (Cardiol J 2013; 20, 2: 112–120)

Key words: blood pressure variability, epidemiology, outcomes, reproducibility, pharmacotherapy

Introduction

Definition and assessment of BPV

Blood pressure (BP) is changing with every heart beat and therefore may vary periodically or accidentally during day, week or in a longer period of time, e.g. season. As BP is labile, it creates a personal condition which is defined as blood pressure variability (BPV). BPV is rather a floating physiological phenomenon than a regular hemodynamic state.

Short- and long-term BPV

There are several ways to express BPV. If BPV is measured continuously from beat-to-beat over an hour or up to 48 h, it is generally called short-term variability and assessed with Fourier analysis. If BP lability is re-assessed occasionally over longer period of time (i.e. visit-to-visit with office or automatic BP measurement), it is called long-term variability. BPV may be evaluated in both normotensive and hypertensive subjects.

Circadian variations in BP

In literature data, the most popular type of BPV is, however, dipping pattern of nocturnal BP. It is assessed on the basis of automatic BP measurement. To categorize BP it is necessary to calculate the night-day BP ratio from 12-h recordings obtained during day and night. Four dipping categories have been already described: extreme dippers (night-day BP ratio $\leq 0.8 \rightarrow$ BP fall at night $> 20\%$ compared to day-time values), dippers (ratio > 0.8 and $\leq 0.9 \rightarrow$ BP fall at night $\geq 10\%$ but less than 20%), non-dippers ($0.9 <$ ratio $\leq 1.0 \rightarrow$ no BP fall or BP fall at night less than 10%) and reverse dippers (or risers) (ratio $> 1.0 \rightarrow$ BP rise at night) (Table 1). In many researches dipping is calculated

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Table 1. Estimation of dipping pattern on the basis of day-time and night-time blood pressure (BP) values.

BP dipping pattern	Night-to-day BP ratio	BP fall at night (compared to day-time)
Extreme dippers	≤ 0.8	≥ 20%
Dippers	(0.8; 0.9]	≥ 10% but < 20%
Non-dippers	(0.9; 1.0]	≥ 0% but < 10%
Reverse dippers	> 1.0	BP rise at night

as BP fall at night of at least 10% (extreme dippers and dippers together) and non-dipping is recognized otherwise. This method of BPV classification is widely used in clinical studies. It is however debatable whether systolic (SBP), diastolic (DBP) or mean BP should be used to estimate the feature. But systolic value is the most common.

In epidemiological and some clinical studies, BPV may be recognized as an individual feature which creates within-person variability. Then it describes BP variation in one person over the definite time interval. Mean or median value is a good estimator of BP value and standard deviation (SD) of the mean (or interquartile range of the median) are indices of BPV. When measures are taken in an individual subject and then collected together to assess mean BP of the group, between-person (person-to-person) variability may be evaluated. Every subject adds its own BP to formulate mean (or median) value of the cohort, and SD (or interquartile range) is a measure of group BPV.

BPV is described either on the basis of ambulatory 24-h BP recordings or office BP measurements. Subjects with the SD below or above the mean BP of the population, measured in day-time or night-time are classified as having low or high BPV. Interquartile range (or SD) of the median is also the acknowledged measure of variation. To combine mean and SD in one value, coefficient of variability (variation) can be calculated according to formula: CV = (SD : mean) × 100%.

As there are few types of BP, different types of BPV exist in clinical setting. In experimental studies the most popular is systolic BPV; DBP is used less frequently. For scientific purposes, we can also distinguish pulse pressure variability (as a difference in systolic and diastolic BPV) or variability of mean BP (as a marker of organ tissue perfusion). Pulse pressure is proportional to stroke volume and constitutes a good marker of aortic stiffness. For that reason pulse pressure variability may become a good index of outcome in patients with advanced aortic arteriosclerosis or labile hypertension. A blunted nocturnal decrease in BP (non-dipping) is also independently associated with increased aortic stiffness in resistant hypertension [1].

It should be underlined that short-term and visit-to-visit BPV, and circadian variations of BP (dipping pattern) are different from physiological point of view and are of different clinical importance. This review will focus on circadian variations of BP which include assessment of the dipping pattern and BP changes measured in a 24-h period using automatic BP monitoring.

Determinants of BPV

Non-dipping pattern may be found in up to 70% of subjects [2–6]. The meta-analysis of 23 studies including 3,476 normotensive patients has revealed that the average night-to-day ratio was 0.87 for SBP and 0.83 for DBP, with ranges across the individual studies from 0.79 to 0.92 for SBP and from 0.75 to 0.9 for DBP [7].

BP fluctuations result from the complex interaction between environmental stimulation, genetic factors and cardiovascular (CV) control mechanisms [8]. It is difficult to identify determinants of BPV because this is an individual trait. It was however found that non-dipping was more frequent is elder subjects [9, 10] and hypertensives, especially those untreated [4, 6, 9]. In the study enrolling 208 treated hypertensive patients [4], the incidence of non-dippers were 3.3 and 2.3 times higher in patients of ≥ 70 and those 60–69 years of age compared to younger counterparts. Non-dipping pattern was statistically significantly 3.7 times more frequent amongst persons with a premature family history of CV disease. Moreover, the incidence of non-dippers was 3.0 and 4.8 times higher in overweight and obese patients compared to those with normal weight, respectively.

On the basis of measurements taken in 621 consecutive patients undergoing ambulatory BP monitoring at the Cleveland Clinic, Brotman et al. [11] have shown that in a statistically significant way non-dippers were older, more likely to be non-white and had higher rates of smoking, diabetes, hypertension, coronary artery disease, congestive failure and renal insufficiency. In registry data en-

rolling 4,765 normotensive and 2,555 hypertensive subjects it has been revealed that after adjustment for potential confounders, the probability of being a non-dipper increased 2.8 times from 30 to 60 years and 5.7 times from 60 to 80 years [9]. Moreover, the risk of blunted nocturnal BP decline was 1.6-folds higher in hypertensive patients compared to normotensives. The problem of BPV is important in children and adolescents in whom early intervention helps to prevent complications of hypertension. Krzych [12] has investigated the issue in 204 consecutive children with essential hypertension. He has found that male sex increased the risk for non-dipping by 2.5 times (OR = 2.45; 95% CI 0.87–6.87; p = 0.08). Gender seems to have no impact on BPV in adults.

Fava et al. [13] investigated heritability of BPV in 118 Swedish families. Nocturnal BP dipping was heritable in 38% for SBP, 9% for DBP and 36% for mean BP. In another study [14], systolic and diastolic nocturnal dipping of more than 10% was heritable in 59% for SBP and 81% for diastolic BPV.

Reproducibility of dipping pattern assessment

The reproducibility of the dipping pattern has been a subject to many researches. The 4-week reproducibility of nocturnal BP fall in untreated hypertensives was rather limited in the study of Cuspidi et al. [15]. Only 75.1% patients (including 78.7% dippers, 67.6% non-dippers and 43.2% extreme dippers) showed no change in their diurnal variations in BP. They have also showed that there were no gender and age-related differences in the repeatability of BP nocturnal fall [16]. Omboni et al. [17] have revealed that in a 4-week period 35–40% of patients became non-dippers if they were dippers (or vice versa) regardless of treatment. In other study [18], when the first 24-h assessment of the dipping pattern was compared to the estimation on the basis of 48-h recording, 11% hypertensive subjects switched patterns, similarly for SBP and DBP and with no difference between treated and untreated patients. In untreated patients with newly diagnosed hypertension, the nocturnal dipping pattern has been repeatable in 82% of them when re-assessed after 4 weeks [19]. Significant intra-subject variations in the diurnal fluctuations in BP have been found by Manning et al. [20] over a 12-month observation. Only 56% of normotensive and hypertensive patients had no change in their dipping status.

There are 3 explanations for those discrepancies in estimation of BPV dipping pattern. First, BPV is a physiological phenomenon and by definition may vary over time. Second, the most appropriate method for defining day and night in published papers is not consistent. Henskens et al. [21] have proven that use of different definitions of awake-sleep and BP indices affected the classification of nocturnal BP dipping significantly, with the repeatability coefficients of no more than 48.7% and kappa values between 0.323 and 0.459. However in the study of Verdecchia et al. [22], the area under the ROC curve of the night-to-time ratio of SBP in the assessment of CV events was comparable when using different clock-dependent or independent definitions of day and night. Additionally, the method of BP measurement is of some importance. Staessen et al. [9] has found that the risk of being a non-dipper was 2.4 times higher for subjects examined with auscultatory vs. oscillometric devices. Third, the impact of treatment, including pharmacotherapy on BPV is also an important point of interest.

Impact of pharmacotherapy on BPV

The potential benefit of bedtime chronotherapy with at least one hypotensive agent was investigated in the MAPEC study [23]. It has been found that despite lack of differences in ambulatory BP between groups of subjects who were randomized either to awakening or bedtime administration of medications, patients from the latter group showed higher sleep-time BP decline and reduced prevalence of non-dipping (34% vs. 62%). In this study, subjects taking more than 1 medication at bedtime showed significantly lower mean sleep-time BP than those ingesting all their medications upon awakening. Those differences were slightly greater for SBP (~ 4.4 mm Hg) than DBP (~ 4.3 mm Hg). The asleep and awake BP were lower for those who were administrated medications at bedtime [23].

Also in the study of Takeda et al. [24] bedtime administration of long-acting antihypertensive drugs helped to restore a proper dipping pattern in 71% of non-dippers. On contrary, only incomplete benefit of antihypertensive therapy on stroke reduction in older hypertensives has been documented [25]. The stroke rates were similar according to medication vs. no-medication in extreme dippers (12% vs. 13%) and reverse dippers (23% vs. 22%), but in non-dippers there was a significantly lower rate in the medicated vs. non-medicated (4.4% vs. 13%) groups. Also in dippers, the stroke rate was lower in the medicated compared to non-medicated (4.7% vs. 8.8%) patients. Kario and Shimada [26]

have revealed that after treatment with calcium channel blocker (CCB), amlodypine, the daytime BP was reduced in dippers, extreme dippers and non-dippers. The night-time BP was significantly lower only in dippers and non-dippers but not in extreme dippers. Additionally, positive correlations were found between baseline BP levels and BP reductions after treatment. In the study enrolling hypertensive subjects [4], compared with patients treated with long-acting CCB, patients treated with angiotensin-converting enzyme inhibitors (ACE) or angiotesin II receptor blockers (ARB) alone were less frequently non-dippers (OR = 0.139; p = 0.01). Subjects treated with joint CCB + ACE or CCB + ARB therapy had tendency of lower incidence of non-dipping (OR = 0.453; p = 0.1). Moreover, those treated with joint therapy including diuretics + CCB and diuretics + ACE or ARB were also of less frequency of non-dipping pattern: OR = 0.378; p = 0.03 and OR = 0.273; p = 0.01, respectively [4]. On the other hand, similar comparison of the effects of ACE inhibitor and CCB in hypertensives [27] has proven that CCB could be more effective, especially in the night-time BP reduction in non-dippers. In a prospective, randomized trial with ACE inhibitor, captopril, it was shown that at the end of the active treatment period, the prevalence of a dipping pattern in the captopril group was more than 7 times higher than in the placebo group [28]. Additionally, the night-to-day ratio and night-time BP load were significantly lower after 4 weeks of treatment with captopril administrated at bedtime.

Mathematic indices, such as trough-to-peak ratio and the smoothness index, represent useful measures of the homogeneity of the antihypertensive effect over 24 h.

Mechanism driving BPV

Neuroendocrine mechanism are major determinants of BP variations responsible also for BP dipping pattern. At the central nervous system, integration of the major driving factors of this temporal variability is mediated by circadian rhythms of monoaminergic systems in conjunction with peripheral level, including the hypothalamic–pituitary–adrenal, hypothalamic–pituitary–thyroid, opioid, renin–angiotensin–aldosterone, endothelial systems and vasoactive peptides [29]. Those humoral secretions are typically episodic, coupled to the circadian endogenous central pacemaker clock, but have some seasonal variations. Sleep induction and arousal are influenced also by many hormones and chemical substances that exhibit 24-h variation (e.g. arginine vasopressin, vasoactive intestinal peptide, melatonin, somatotropin, insulin, steroids, serotonin, corticotropin-releasing factor, adrenocorticotropic hormone, thyrotropin-releasing hormone, endogenous opioids, and prostaglandin E2), all with established responsiveness in the CV system. As a consequence, physical, mental, and pathologic stimuli that activate or inhibit neuroendocrine effectors of biological rhythmicity may also interfere with, or modify, the temporal BP structure. Moreover, immediate adjustment to exogenous components/environment demands by BP rhythms is modulated by the circadian-time-dependent alertness of biological oscillators and their neuroendocrine effectors [29].

Alteration in autonomic function plays the pivotal role in creating BPV [30] and non-dippers are characterized with an abnormal pattern of autonomic activity with higher sympathetic and lower parasympathetic modulation [31–32]. The reverse dipping state has been recognized to be related with a sympathetic activation greater for magnitude that seen in the other conditions displaying abnormalities in night-time BP pattern [33]. It has been also found that autonomic neuropathy is the pivotal factor of blunted nocturnal fall in BP in both type 1 and 2 diabetic patients [34], also in non-insulin-dependent diabetic subjects [35]. The study investigating autonomic nervous system activity in essential hypertension has documented that impaired CV reflexes might contribute to the decreased sympathovagal balance in non-dippers [36]. Additionally, Kario et al. [37] concluded that diurnal BP variation in elderly hypertensive patients could be associated with factors regulating circulating blood volume and impaired sensitivity of adrenergic reactivity. Night-time alpha-adrenergic blockade with doxazosine may markedly affect the nocturnal BP dipping status of hypertensives with grater reduction observed in non-dippers and risers than dippers [38].

Additional evidence is given by studies investigating the impact of physical activity on BPV. Physical activity is one of the determinants of ambulatory BP and its diurnal variations [39]. This effect has been investigated by Cavelaars et al. [40]. They have documented that non-dippers differed from dippers by an increase of vascular resistance during the night, and the degree of physical activity normally encountered during ambulatory monitoring had little influence on the diurnal BP profile or dipping status. The impact of time of day for exercise on BP dipping pattern in hypertensives has been investigated by Park et al. [41]. In this

Table 2. Mechanisms with significant impact on altered blood pressure variations.

Mechanism	Explanation
Autonomic nervous system dysfunction	Impaired vascular reflexes Improper adrenergic stimulation
Inflammation	↑C-reactive protein concentration
Endothelial dysfunction	Hemostatic imbalance (↑D-dimer, ↑plasminogen activator inhibitor-1, ↑intercellular adhesion molecule-1)
Metabolic imbalance	Strict relationship with the number of metabolic syndrome components Hyperglycemia favors blood pressure variations

study, non-dippers responded to exercise irrespectively of time of day and non-dippers responded to exercise differently than dippers. Evening exercise exhibited a greater reduction in SBP at night in non-dippers than dippers and morning exercise had similar effect on day-time and 24 h SBP reduction both in dippers and non-dippers. Furthermore, the duration of the BP reduction persisted up to 24 h after exercise [41].

The influence of day-time activity of BPV merits further description due to ambiguous existing researches' findings. Investigating impact of aerobic exercise on the circadian BPV, no effects were observed either for SBP or DBP in young healthy subjects [42]. In 39 untreated hypertensives, Mansoor et al. [43] found poor overall correlation between BP and activity level with marked between-subject variability in the strength of association. Moreover, almost similar results were revealed for dippers and non-dippers. On the contrary, Izdebska et al. [44] have shown that after a non-standardized 3-month moderate aerobic training, mildly hypertensive young adults had a statistically significant decrease in SBP variations compared to healthy normotensive counterparts. Those findings are in agreement with Narkiewicz et al. [45] who confirmed that there is a significant positive interaction between sympathetic traffic and day-time BPV, and in normotensive males greater BP decline at night was related to the greater activity during day-time.

Taking altogether, it is however clear that baseline BP condition should be taken into account in data interpretation.

The issue of inflammation and metabolic imbalance are also of great importance in the pathogenesis of abnormal BP variations. Essential hypertensive non-dippers compared to dippers have been found to exhibit higher high-sensitive C-reactive protein values [46]. Furthermore, ambulatory and nocturnal systolic BP fall interrelated and participated in the inflammatory process that accompanied non-dipping pattern. Reactive oxygen species formation was significantly increased in extreme dippers [47]. In non-dippers however interruption in hemostastic condition has also been noticed [48], with the increase in D-dimer, plasminogen activator inhibitor-1 and intercellular adhesion molecule-1 concentrations.

Subjects with metabolic syndrome have an increased prevalence of abnormal dipping pattern as the number of metabolic syndrome components rise [49]. Patients with metabolic syndrome are more frequent non-dippers (38.9% vs. 24.5%) and reverse dippers (6.3% vs. 3.3%) and less frequently dippers (43.5% vs. 54.4%) or extreme dippers (11.3% vs. 17.8%) compared to patients without this metabolic imbalance [50]. Non-dipping pattern has been found to correlate with glucose intolerance [51]. Hyperglycemia may also be associated with abnormal diurnal BP variation [52] but interestingly, insulin resistance failed to be connected with nocturnal BP dipping in obese hypertensives [53] (Table 2).

Clinical consequences of abnormal BP variations

Blood pressure variations may contribute to prognosis. The dipping pattern and the night-day BP ratio significantly predicted mortality and CV events in hypertensive patients with [54] and without [55, 56] history of major CV disease, even after adjustment for BP values. Fagard et al. [54] have found in the former group that the outcome was worse in reverse dippers and non-dippers compared to dippers, and in the latter population [55, 56] the incidence of CV events was higher only in reverse dippers, whereas mortality was lower in extreme dippers. Additionally, the systolic night-day BP ratio independently predicted all-cause mortality and CV events. Those findings were

confirmed regardless of gender, age and history of treatment of hypertension. Over a 10-year follow--up of persons with or without hypertension, Li et al. [57] have confirmed that the night-day BP ratio was a strong predictor of all-cause mortality but no association was found for CV events. Also in the multi-center study of Boggia et al. [58], the night-day ratio predicted mortality but not fatal combined with non-fatal events in a cohort of 7,458 subjects. In the Syst-Eur Trial of over 800 elder patients randomized to active treatment of hypertension (nitrendipine + enalapril and/or hydrochlorothiazide) or to placebo [9], CV risk increased with a higher night-day BP ratio of SBP (HR = 1.41 per 10% increase) only in a placebo group. In the same cohort of patients, the risk of stroke increase by 80% for every 5 mm Hg increase in night-time systolic BPV [59]. The night--day BP ratio is also a useful indicator providing significant prognostic information in patients with end-stage renal disease [60] and extreme dippers with chronic kidney disease had a 2.6-fold higher risk of CV events [61]. Rahman et al. [62] have shown that hemodialysis patients were usually non-dippers and the degree of decline in nocturnal BP was independently associated with left ventricle hypertrophy.

A detailed insight into the impact of circadian BP fluctuations on prognosis was the main goal of the MAPEC study. Hermida et al. [23, 63] prospectively studied 3,344 patients who were randomized into group of subject ingesting at least one hypotensive agent at bedtime or not. In the whole study population only asleep SBP was a significant predictor of outcome (any CV events, including CV morbidity and mortality). Even after adjustment for potential confounders, the CV risk decreased by 17% for every 5 mm Hg decrease in asleep SBP. The reduced risk was confirmed for both subjects with either normal (HR = 0.81) or elevated BP (HR = 0.84). For those with high BP, reduction in the risk was different if all medications were given on awaking (HR = 0.76) or at bedtime (HR = 0.67). After a 5.6-follow-up subjects ingesting at least one BP-lowering agent at bedtime exhibited a significantly lower risk of all CV events (RR = 0.39) and major events (RR = 0.33) than those taking all drugs upon awaking. Noteworthy, non-dippers more frequent amongst CV event-subjects than dippers (73% vs. 46%, $p < 0.001$).

A blunted reduction in nocturnal BP and high variations in diurnal BP may play a pivotal role in the development of target organ damage in essential hypertensive patients, including left ventricle hypertrophy and intima media thickening [64–66]. Regardless of BP values, never-treated hypertensive non-dippers have shown a significantly greater extent of target organ damage compared to dippers [67]. The measures of target organ damage were left ventricular mass index, interventricular septum thickness, left atrium and aortic root diameters. Those findings have been confirmed recently by Ivanovic et al. [68]. Patients with abnormal diurnal BP variation patterns (non-dippers, extreme dippers and reverse dippers) have also showed higher plasma BNP levels than those with normal BPV [69] and reverse dippers had higher microalbumin and micoglobulin excretion, and albumin/creatinine ratio [70].

Blunted reduction of systolic and diastolic night-time BP has been found to be associated with poorer cognitive performances estimated on the basis of the Mini Mental State Examination [71]. Moreover Guo et al. [72] has documented that mild cognitive impairment was more frequent in extreme dippers (32%), non-dippers (30%) and risers (50%) than in dippers (13.2%).

Furthermore, in resistant hypertension, the non-dipping pattern has been shown to be an independent predictor of CV mortality and the composite end point of fatal or non-fatal CV events, all-cause mortality and CV mortality [73, 74]. Non--dippers and reverse dippers were also at increased risk of CV events [73–75]. Also, non-dipping and reverse dipping were relatively common patterns of circadian BPV seen in acute stroke patients [76]. Additional data is given by Bastos et al. [77] who have revealed that compared to treated hypertensive subjects with no history of cerebral events, those with previous stroke or transient ischemic attack were more frequently extreme dippers (10.6% vs. 6.3%), non-dippers (48.9% vs. 41.7%) and reverse dippers (12.8% vs. 7.6%). Moreover, patients with hypertension who suffered from any coronary event in the past were also more frequently non-dippers (56.3% vs. 43%) and reverse dippers (18.8% vs. 5.9%) [77]. CV events were more frequent also in hypertensive non-dippers aged 65 years or less [10] and in reverse dippers with or without diabetes type 2 [78]. In a 9-year follow-up study [79], type 2 diabetic patients with non-dipping pattern were at higher risk of death as compared to dippers. Non-dippers with diabetes are at increased risk of death, regardless of diabetes type [80], and the combination of non-dipping and subsequent renal impairment leads to the highest mortality rate. Reverse-dipping status in hypertensive diabetics almost 3 times (HR = 2.79) increased the risk of CV events but the effect disappeared after adjustment for 24-h BP. Abnormal BP dipping

status has been documented to increase risk of death or hospitalization for heart failure exacerbation [81] and non-dipping pattern has been associated with an over 2-times higher risk of congestive heart failure in initially healthy Finish male [82]. Finally, non-dippers with sustained hypertension have been found to be at a 2-fold higher risk of developing atrial fibrillation than dippers [83].

On the other hand, no association between nocturnal decline in BP and mortality has been found in the Ohasama cohort study [84]. Although both nocturnal hypotension and erratic diastolic BPV assessed by Fourier spectral analysis predicted mortality, subsequent study of the PAMELA data has failed to prove any relationship between the risk of death and 24-h, day-time and night-time BPV expressed as SDs [85]. Also in the study of Hansen et al. [86, 87] recruiting subjects from 11 populations, there was no prognostic value of reading-to-reading BPV and in the study of Gavish et al. [88] there was no ability of the BPV to predict the outcome on the basis of the ratio of 24-h ambulatory systolic BPV to diastolic variability.

Finally, recent findings designate that the mean nocturnal BP value is the most sensitive predictor of cardio- and cerebrovascular morbidity, and mortality [89–90]. Moreover, regardless of the relative circadian BP values, insufficient BP fall at night compared to day-time level or a high night to day BP ratio is associated with poor prognosis [89, 90].

Conclusions

Blood pressure variability is a classical physiological phenomenon as BP varies individually continuously and episodically. In healthy subjects, BPV is a measure of hemodynamic condition and reflects function of autonomic nervous system. BP fluctuations result from the complex interaction between environmental stimulation, genetic factors and CV control mechanisms. Abnormal BPV is recognized in persons with a blurred dipping pattern (i.e. extreme dipping, non-dipping, reverse-dipping, morning surge of BP) or increased variations of day--time or nigh-time BP (high BP lability). Inappropriate BP decline at night worsens the outcome, including increase in all-cause and cardiac mortality and incidence of CV events, and advance in target organ damage. Abnormal BPV may be softened or removed with suitable time-dependent administration of anti-hypertensive agents, especially those acting on the renin–angiotensin system.

Conflict of interest: none declared

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